Phylogenetically, all living organisms harbour biochemical pathways devoted to the repair of potentially mutagenic lesions. The diversification process is not confined to the coding regions of the genome but instead depends on a process of localized gene diversification and provides the high diversity of antigen-binding molecules that is required to recognize and combat the enormous range of invading pathogens.

The primary repertoire of antibodies and T-cell receptor molecules in man is not encoded in the germ line but instead depends on a process of programmed gene rearrangement where, following targeted introduction of double-stranded DNA breaks by the RAG1/2 endonuclease, segmental gene recombination is used to assemble a diverse family of antigen receptor molecules.

RAG-mediated gene rearrangement does not, however, yield a large enough repertoire to provide high-affinity antibodies to the vast range of antigens encountered. The primary repertoire of antibodies that is generated by RAG-mediated gene rearrangement is enormously increased by somatic hypermutation. Nucleotide substitutions are introduced into the region of the DNA that encodes the antigen-combining site of the antibody, and variant antibodies are then selected based on their affinity for antigen. Somatic hypermutation is not the only means by which the primary repertoire is diversified: in chickens as well as some other vertebrates segmental gene conversion templated by donor pseudogenes plays a major role.

The diversification process is not confined to the gene segments encoding the antigen-combining site of the antibody. During an immune response, there is also a shift from the production of IgM antibody to the production of other antibody classes (IgG, IgA and IgE). This shift in immunoglobulin isotypes is achieved by class switch recombination, a process of localized (region-specific but not site-specific) non-homologous DNA recombination.

Although our understanding of RAG-mediated gene rearrangement is relatively well advanced, the mechanisms underpinning somatic hypermutation, gene conversion and class switch recombination have long been an enigma. A major breakthrough came with the demonstration that AID (activation-induced deaminase, a protein with sequence homology to cytidine deaminases present in B lymphocytes) was essential for all three processes. It has subsequently become apparent that AID acts by deaminating cytosines within the immunoglobulin locus with the different processes of antibody gene diversification resulting from the usage of different pathways for resolving the AID-generated U : G mismatch. That is, proteins have been co-opted from the base excision repair, mismatch repair and non-homologous end-joining pathways to deal with dU residues and DNA strand breaks.

As a consequence of rapid recent advances, AID-mediated antibody diversification is the best characterized of the physiological processes of programmed DNA deamination. But it is not the only example. In the same way that Honjo and colleagues identified AID by analysing differential gene expression patterns using a procedure of subtractive hybridization (Muramatsu et al. 1999), so Malim and colleagues identified APOBEC3G as a protein implicated in host restriction of HIV-1 (Sheehy et al. 2002). As AID, the APOBEC3 proteins also deaminate cytosine in DNA. But in the case of several APOBEC3s analysed, the physiological target is lentiviral replication intermediates rather than cellular DNA. It is clear that such deamination initiates the generation of hypermutated HIV sequences, although the precise role of this deoxycytidine deamination in lentiviral restriction remains to be fully elucidated.

It has been known for many years that deamination of adenosine to yield inosine in RNA is a critical step in tRNA maturation across the biological universe. It has also been widely appreciated that cytosine deamination plays a role in mRNA editing. This appears widespread in trypanosomes but, so far as is known, in man is restricted physiologically to the unique example of apolipoprotein B RNA where it is catalysed by a complex comprising APOBEC1. Ten years ago, however, there was no indication that deamination of bases in DNA played any role in programmed genomic change. The advance was in large part triggered by the identification of the critical role of AID in antibody gene diversification, a result first communicated at the Royal Society by Professor Honjo as late-breaking news during a Discussion Meeting on Hypermutation in antibody genes in July 2000.

The meeting now covered by this volume was held at the Royal Society in June 2008 and provided an opportunity to discuss and reflect upon the enormous
advances that had been made since the landmark discovery of AID. Back in 2000, the homology of AID to APOBEC1 led to the initial suggestion that AID would act through RNA editing. As is evident from the presentations at this meeting, there is now near but not quite universal acceptance that AID works through targeting deoxycytidines in immunoglobulin gene DNA. Considerable progress has also been made in identifying the pathways that lead from the AID-generated U : G mismatch to the resultant patterns of immunoglobulin gene diversification. Thus, for example, at the Discussion Meeting in 2000, much attention was devoted to a consideration of the multiple translesion DNA polymerases that might play a role in somatic hypermutation. By the time of the current meeting, it was clear that DNA polymerase η was the enzyme playing a lead role in hypermutation at A : T pairs, but discussion had moved to considering precisely how this polymerase was recruited following AID-mediated DNA deamination.

With regard to AID itself, much work has been done on its expression and localization. It has indeed been shown to be able to deaminate cytosine in single-stranded DNA in vitro, but it remains a difficult protein to work with biochemically, owing to aggregation and poor solubility: its three-dimensional structure is still unknown. The oligomeric nature of AID in vitro also remains undefined, and little is understood as to how it is targeted to its DNA substrate or to how its nuclear trafficking is regulated although several associations (such as with RPA or CTNNBL1) were discussed at the meeting.

The consequences of mis-targeted action of AID are potentially oncogenic. Results were presented from several laboratories, which focused on the multiple levels of regulation of AID activity (including both miRNA-mediated and post-translational regulation), on the mechanisms of AID-mediated oncogene translocations, and on the repair of AID-induced lesions.

The similar biochemical activities of AID and APOBEC3s have also revealed a wholly unexpected parallel between pathways in adaptive and innate immunity. Indeed, it was entirely unanticipated that hypermutation of HIV-1 and hypermutation of antibody genes derive in part from very similar initiating events, deamination of cytosine in DNA. However, whereas the mutagenic activity of AID is central to its physiological function, presentations at the meeting revealed that the precise contribution of cytosine deamination to the functions of APOBEC3s as viral restriction factors remains a topic for future clarification.

Although the major aspect of their physiological mechanism of action remains ill defined, APOBEC3 proteins are potential factors that can assist in limiting the spread of HIV, especially if their degradation by the virally encoded Vif gene product can be prevented. It is likely that there will also be increased clinical and biotechnological interest in AID since it may well provide an attractive target in situations where it is desired to inhibit immunoglobulin class switching (e.g. to prevent IgE-mediated allergy) or antibody maturation (e.g. antibody-mediated autoimmune disease).

Apart from the formal presentations themselves, the meeting benefited from lively and extensive discussion, ably inspired and coordinated by the session chairs (which included Prof. Alan Lehmann, Prof. Joe Jiricny and Prof. Robin Weiss, FRS). We thank all those who contributed to the meeting, which not only revealed how rapidly the field had advanced since its birth at the Discussion Meeting in 2000, but also how much more still remains to be learned.

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